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(54) A solid pharmaceutical preparation for dialysis and a process for producing the same

Feste pharmazeutische Zubereitung für die Dialyse sowie Verfahren zu deren Herstellung

Préparation pharmaceutique solide pour la dialyse et son procédé de fabrication

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DescriptionField of the Invention

- 5 [0001] The present invention relates to a solid pharmaceutical preparation for dialysis and, more particularly, to a solid dialysate concentrate for preparing a dialysis solution containing sodium hydrogencarbonate and a process for producing the same.

Background of the Invention

- 10 [0002] When hemodialysis is carried out for a patient suffering from weakened hepatic function, the blood of the patient is cleaned in an artificial kidney. Generally, a dialysis solution is perfused in this artificial kidney and contacted via a dialysis membrane with the blood of the patient so that wastes in the blood are transferred to the dialysis solution. As this dialysis solution, an acetate dialysis solution has been used widely but has recently been substituted with a 15 dialysis solution containing sodium hydrogencarbonate (i.e., sodium bicarbonate) drastically reducing unpleasant symptoms during dialysis.

- 20 [0003] The dialysis solution containing sodium bicarbonate is usually prepared from two kinds of dialysis solution, that is, a pharmaceutical preparation (referred to hereinafter as composition A) containing electrolytes (e.g., sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and sodium acetate) and a pH adjusting agent (e.g., acetic acid) and a pharmaceutical preparation (referred to hereinafter as composition B) containing sodium bicarbonate. These dialysis solutions may contain sugars such as glucose or may be mixed with another pharmaceutical preparation containing sugars.

- 25 [0004] Heretofore, compositions A and B were commercialized in the form of a concentrated solution prepared at a predetermined concentration and used by the customer after being diluted with water. However, about 300 L perfusion solution of sodium hydrogencarbonate is necessary for the dialysis of one patient, and thus in conducting dialysis treatment of a large number of patients, a large quantity of the concentrated solution must be used and diluted with water. Accordingly, there are recently many cases where composition B prepared in a powdery form is used to reduce the burden on those who prepare the dialysis solution and to reduce storage space. In this connection, a pharmaceutical preparation for dialysis consisting of two compositions has been developed, one of which is a pulverized composition 30 A while other is also usually a pulverized composition B, and a solid pharmaceutical preparation for dialysis consisting of all ingredients necessary for dialysis as one composition, namely a granulated or powdered solid dialysate concentrate, has also been developed.

- 35 [0005] As the one composition type of solid pharmaceutical preparation for dialysis, there are disclosed those obtained by mixing all ingredients necessary for a dialysis solution in the form of granules or powders, or by coating essential ingredients on a nucleating particle (Japanese Patent No. 2846883, Japanese Patent No. 2739898 and JP-A 10-259133). However, these pharmaceutical preparations suffer from the problem that since sodium bicarbonate, calcium salt and magnesium salt are directly contacted with one another, these ingredients react with crystallization water contained in the calcium salt and magnesium salt, or with moisture in the air, to form sparingly soluble salts. In addition, there is another problem that since sodium bicarbonate and acetic acid are directly contacted with each other, these 40 ingredients react with each other to generate carbon dioxide, with the result that the pH of the dialysis solution can not be maintained in a suitable range (Japanese Patent No. 2846883 and Japanese Patent No. 2739898).

- 45 [0006] On one hand, a solid pharmaceutical preparation for dialysis comprising sodium bicarbonate in an innermost layer and sodium diacetate as an acid in an outermost layer (JP-A 10-259133) may generate carbon dioxide upon decomposition of sodium bicarbonate in the innermost layer by heat or water added in later steps. Further, the water and heat generated from the decomposition of sodium bicarbonate cause decomposition of glucose in the solid pharmaceutical preparation for dialysis. Moreover, acetic acid which has been bound to sodium acetate in sodium diacetate is easily released therefrom, and this acetic acid reacts with sodium bicarbonate to generate carbon dioxide and then the pH of the dialysis solution can not be maintained in a suitable range.

- 50 [0007] In consideration of these disadvantages, some solid pharmaceutical preparations for dialysis consisting of all ingredients necessary for dialysis as one composition are developed. In one pharmaceutical preparation, sodium bicarbonate and an organic acid, or sodium bicarbonate and calcium salt or magnesium salt are layered such that both of them are not contacted with each other and reaction therebetween is prevented (JP-A 6-335527, JP-A 8-169836, JP-A 8-92071 and JP-A11-114054). Another solid pharmaceutical preparation for dialysis consisting of all ingredients necessary for dialysis as one composition is produced by granulating calcium salt, magnesium salt and solid organic acid together, but separately granulating sodium bicarbonate, and then mixing the above granulated ingredients and the granulated sodium bicarbonate (JP-A 6-335528 and JP-A 8-92070).

- 55 [0008] In these solid pharmaceutical preparations for dialysis, however, it is likely that if pH adjusting agents, i.e., a solid organic acid and sodium acetate, are contacted with each other, the solid organic acid reacts with sodium acetate

to form free acetic acid, and the vaporized acetic acid reacts with sodium bicarbonate to generate carbon dioxide. Further, the respective ingredients to be coated on nucleating particles of electrolytes in the solid pharmaceutical preparations for dialysis must be finely pulverized by a sample mill and as a result, not only the steps but also the time for producing the preparation are increased. Additionally, a solid pharmaceutical preparation for dialysis having an outermost layer, which under drying and by spraying with water or an aqueous solution, has been coated with a fine powder obtained by pulverizing a mixture of sodium bicarbonate, sodium chloride and other electrolytes (JP-A 11-114054), contains a large amount of the powder and requires a longer time for coating and drying thereof such that the sodium bicarbonate may be decomposed by long-time heating.

[0009] In addition, there is also known a solid pharmaceutical preparation for dialysis consisting of all ingredients prepared by mixing calcium salt, magnesium salt, solid organic acid, sodium bicarbonate and glucose coated respectively with sodium citrate (JP-A 10-87478), or a solid pharmaceutical preparation for dialysis consisting of all ingredients prepared by mixing calcium salt, magnesium salt, solid organic acid and sodium bicarbonate coated respectively with sodium chloride and/or potassium chloride (JP-A 10-330270). However, it is difficult to attain uniformity of the ingredients in the solid pharmaceutical preparations for dialysis because the solid organic acid as an ingredient added in a small amount, the calcium salt and magnesium salt are respectively mixed in the form of powder.

Summary of the Invention

[0010] Under these circumstances as described above, the object of the present invention is to provide a solid pharmaceutical preparation for dialysis consisting of all ingredients as one composition, which is excellent in the uniformity of the ingredients therein, is capable of preventing not only a reaction between sodium bicarbonate and an solid organic acid, or sodium bicarbonate and electrolytes, but also a reaction between a solid organic acid and sodium acetate, and does not require further pulverization of the ingredients.

[0011] As a result of their eager study for solving the problems described above, the present inventors have found that a solid pharmaceutical preparation for dialysis which comprises a granule or powder with a plurality of layers of sodium acetate, solid organic acid and sodium bicarbonate separated respectively and, preferably, which are coated with glucose and sodium bicarbonate in the form of non-pulverized crystals therein, achieves the intended object, thus arriving at the present invention.

[0012] That is, the present invention relates to a solid pharmaceutical preparation for dialysis comprising an electrolyte for hemodialysis, a solid organic acid and glucose is characterized by comprising a plurality of layers which are separated from each other on the surface of a nucleating particle consisting of sodium chloride, wherein the plurality of layers include a layer (A) comprising sodium acetate but not containing the solid organic acid, a layer (B) comprising the solid organic acid but not containing sodium acetate, and a layer (C) comprising sodium bicarbonate.

[0013] Further, the present invention relates to a process for producing a pharmaceutical preparation for dialysis, which comprises forming a layer (A) containing sodium acetate but not containing solid organic acid on the surface of a nucleating particle, and forming a layer (B) containing solid organic acid and separated from the layer (A) on the surface of the nucleating particle, and forming a layer (C) containing sodium bicarbonate and separated from the layer (B) on the surface of the nucleating particle in this order.

[0014] In one embodiment of the present invention, the solid pharmaceutical preparation for dialysis comprises a nucleating particle consisting of sodium chloride, a first layer formed on said nucleating particles and containing sodium acetate but not containing a solid organic acid as layer (A), a second layer containing at least one compound selected from the group consisting of calcium chloride, magnesium chloride, potassium chloride and sodium chloride but not containing sodium acetate or a solid organic acid, a third layer containing a solid organic acid but not containing sodium acetate as layer (B), a fourth layer containing glucose powder and a fifth layer containing sodium bicarbonate powder as layer (C) in this order.

[0015] One embodiment of the process in the present invention comprises,

- (a) spraying an aqueous solution containing sodium acetate but not containing a solid organic acid on the surface of nucleating particles consisting of sodium chloride, and drying the particles,
- (b) spraying the particles obtained in step (a) with an aqueous solution containing at least one compound selected from the group consisting of calcium chloride, magnesium chloride, potassium chloride and sodium chloride but not containing sodium acetate and not contacting a solid organic acid, and drying the particles,
- (c) spraying the particles obtained in step (b) with an aqueous solution containing a solid organic acid and not containing sodium acetate and drying the particles,
- (d) mixing glucose powder with the particles obtained in step (c), then spraying the particles with an aqueous solution containing glucose and/or sodium chloride and drying particles, and
- (e) mixing sodium bicarbonate powder with the particles obtained in step (d), then spraying the particles with an aqueous solution containing glucose and/or sodium chloride and drying the particles.

Brief Description of the Drawings**[0016]**

- 5 Fig. 1 is an illustration showing the process for producing the solid pharmaceutical preparation for dialysis according to the present invention.
 Fig. 2 is an electron micrograph ($\times 200$) of a cubic crystalline particle of sodium chloride.
 Fig. 3 is an electron micrograph ($\times 150$) of a particle of sodium chloride obtained by spraying the particle with an aqueous sodium acetate solution and drying it.
 10 Fig. 4 is an electron micrograph ($\times 150$) of a particle obtained by spraying the surface of the particle shown in Fig. 3 with an aqueous mixture of calcium chloride, magnesium chloride and potassium chloride, and then drying it.
 Fig. 5 is an electron micrograph ($\times 150$) of a particle obtained by spraying the surface of the particle shown in Fig. 4 with an aqueous solution of citric acid, and then drying it.
 Fig. 6 is an electron micrograph ($\times 50$) of a particle obtained by mixing glucose powder with the particle shown in Fig. 5, spraying it with an aqueous solution containing glucose and sodium chloride, and drying it.
 15 Fig. 7 is an electron micrograph ($\times 60$) of a particle obtained by mixing sodium bicarbonate powder with the particle shown in Fig. 6, spraying it with an aqueous solution containing glucose and sodium chloride, and drying it.
 Fig. 8 is an electron micrograph ($\times 400$) of a part of a section of the particle shown in Fig. 7.

20 Embodiment of the Invention

[0017] The order of coating multiple layers in the present invention is not limited but certain layers are necessarily separated from each other in order for these layers not to contact each other directly. One of the methods for separating these layers preferably comprises providing an intermediate layer containing an electrolyte for hemodialysis excluding sodium acetate, and glucose between the layers (A), (B) and (C). The layer (C) containing sodium bicarbonate is preferably provided as an outer layer and, preferably, the outermost layer of the preparation because it is feared that the outer layer may be decomposed by the heat or moisture added in the manufacturing process.

[0018] In the present invention, the nucleating particles consisting of sodium chloride are crystals with a particle diameter of about 0.1 to 1.0 mm and a water content of about 0 to 0.1 %. The water content is expressed in terms of loss (%) in weight of said compound upon drying at 80 °C for 3 hours and does not include water of crystallization in said compound.

[0019] An electrolyte for hemodialysis in the present invention includes sodium chloride at least forming a nucleating particle, calcium chloride, magnesium chloride, potassium chloride, sodium acetate, and sodium bicarbonate, and may include other electrolytes such as potassium acetate, calcium gluconate, calcium citrate. Said magnesium chloride includes magnesium chloride- $6\text{H}_2\text{O}$, etc, and said calcium chloride includes calcium chloride- $2\text{H}_2\text{O}$ or calcium chloride- $1\text{H}_2\text{O}$, etc. The sodium acetate includes sodium acetate anhydride, sodium acetate- $3\text{H}_2\text{O}$, etc.

[0020] The solid organic acid in the present invention includes pharmaceutically acceptable solid organic acids, for example, citric acid, oxalic acid, tartaric acid, maleic acid, ascorbic acid, oxaloacetic acid, isocitric acid, malic acid. The organic acid is preferably citric acid.

[0021] In the present invention, glucose is preferably in the form of powder with a particle diameter of about 0.01 to 0.5 mm and a water content of about 0 to 1 %. For simplification of the granulation step, it is more preferably in the form of non-pulverized crystals with a particle diameter of 0.03 to 0.5 mm. Said glucose may contain another sugar ingredient, such as maltose, xylitol, trehalose, etc.

[0022] In the present invention, sodium bicarbonate is preferably in the form of powder with a particle diameter of about 0.01 to 0.5 mm and a water content of about 0 to 0.1 %. For simplification of the granulation step, it is preferably in the form of non-pulverized crystals with a particle diameter of 0.03 to 0.5 mm.

[0023] The solid pharmaceutical preparation for dialysis according to the present invention is preferably a multilayered particle consisting of a nucleating particle and 5 layers consisting of first to fifth layers on said nucleating particle. A group of preferable compounds forming each layer in said particles is as follows:

- 50 Nucleating particles: sodium chloride
 First layer (layer A): sodium acetate
 Second layer: calcium chloride, magnesium chloride, potassium chloride and sodium chloride
 Third layer (layer B): solid organic acid
 55 Fourth layer: glucose and sodium chloride
 Fifth layer (layer C): sodium bicarbonate and sodium chloride

[0024] The solid pharmaceutical preparation for dialysis according to the present invention is a coated particle pro-

viding the layers (A), (B) and (C) separated, respectively, as described above, and it is thereby not only possible to prevent sodium bicarbonate and the solid organic acid, and sodium bicarbonate and the electrolyte, from being contacted with each other but is also possible to prevent the solid organic acid and sodium acetate from being contacted with each other.

- 5 [0025] In 1 kg of the solid pharmaceutical preparation for dialysis according to the present invention, e.g., the following ingredients are contained in the following amounts.

10	Sodium chloride	532 to 760 g
	Sodium acetate	15 to 98 g
	Potassium chloride	7 to 22 g
	Calcium chloride (2H ₂ O)	15 to 29 g
	Magnesium chloride (6H ₂ O)	5 to 20 g
15	Sodium bicarbonate	168 to 336 g
	Citric acid	13 to 32 g
	Glucose	100 to 200 g

- 20 [0026] The solid pharmaceutical preparation for dialysis according to the present invention is dissolved in water to prepare a dialysis solution. The dialysis solution has, e.g., the following composition (final concentration).

25	Na ⁺	130 to 150 mEq/L
	K ⁺	1.0 to 3.0 mEq/L
	Ca ²⁺	2.0 to 4.0 mEq/L
	Mg ²⁺	0.5 to 2.0 mEq/L
30	Cl ⁻	100 to 125 mEq/L
	CH ₃ COO ⁻	2 to 12 mEq/L
	HCO ₃ ⁻	20 to 40 mEq/L
	Citric acid	2.0 to 5.0 mEq/L
	Glucose	100 to 200 mg/dL

The contents in the solid preparation for dialysis according to the present invention can be easily made uniform by dissolving the ingredients added in a small amount, that is, sodium acetate, potassium chloride, calcium chloride, magnesium chloride and the solid organic acid in water to form an aqueous solution to be used as coatings.

- 35 [0027] The other ingredients added in a large amount, that is, sodium chloride, glucose and sodium bicarbonate are used in the form of powder, nucleating particles or a coating layer whereby the granulation step is simplified. Glucose and sodium bicarbonate are used preferably in the form of non-pulverized crystalline powder.

[0028] The solid pharmaceutical preparation for dialysis according to the present invention can be produced by centrifugal fluid granulation, rotating granulation, fluidized-bed granulation or a combination thereof.

- 40 [0029] The solid pharmaceutical preparation for dialysis in the present invention is a coated particle providing the above layers (A), (B) and (C) respectively separated. It is manufactured by coating the layer (A) containing sodium acetate but not containing solid organic acid on the nucleating particles consisting of sodium chloride, coating a layer (B) containing solid organic acid but not containing sodium acetate on the layer (A) but separated from this layer (A), and then, coating a layer (C) containing sodium bicarbonate on the layer (B) but separated from this layer (B).

- 45 [0030] Hereinafter, the process for producing the pharmaceutical preparation for dialysis according to the present invention is described by reference to the drawings.

[0031] Fig. 1 is an illustration showing the process for producing the pharmaceutical preparation for dialysis according to the present invention. The product obtained in each step is not limited to the form shown in Fig. 1.

- 50 (1) First, 900 to 1,400 g sodium chloride with a particle diameter of 0.1 to 1.0 mm serving as nucleating particles are introduced into a granulation drying unit for rotatively fluidizing. The particles are sprayed with 200 to 400 ml of an aqueous solution containing 60 to 130 g sodium acetate and then dried to form a first layer of 1 to 10 µm in thickness thereon. At least a part of the surface of the sodium chloride as nucleating particles is coated with said sodium acetate. The spraying method involves spraying the particles with the aqueous sodium acetate solution at a rate of 8 to 30 ml/min. for 7 to 50 minutes. The drying is preferably continued at 70 to 90 °C during the above spraying. The water content in the granulated product after drying is preferably 0.1 to 2.0 %.
- 55 (2) The granulated product obtained in step (1) is sprayed with 80 to 250 ml of an aqueous solution containing 25

to 50 g calcium chloride, 15 to 30 g magnesium chloride and 10 to 40 g potassium chloride for 5 to 40 minutes at a rate of 7 to 15 ml/min. and then dried at 70 to 90 °C to form a second layer of 1 to 10 µm in thickness thereon. Sodium chloride as nucleating particles and sodium acetate contained in the first layer are coated with the second layer. For the purpose of separating sodium acetate contained in the first layer from the organic acid contained in the third layer and thickening the second layer, said aqueous solution may contain sodium chloride. Further, the second layer may be made of plural layers by spraying the particles with an aqueous solution containing calcium chloride and magnesium chloride, drying the particles, spraying the particles with an aqueous solution containing potassium chloride and drying the particles. The water content in the granulated product after drying is preferably 0.1 to 2.0 %.

(3) The granulated product obtained in step (2) is sprayed with 40 to 150 ml of an aqueous solution containing 20 to 50 g solid organic acid for 3 to 30 minutes at a rate of 4 to 10 ml/min. and is then dried at 70 to 90 °C to form a third layer of 1 to 5 µm in thickness thereon. The various electrolytes contained in the second layer are coated with the third layer. The water content in the granulated product after drying is preferably 0.1 to 2 %.

(4) 130 to 300 g glucose powder with a particle diameter of 0.03 to 0.5 mm is introduced into, and mixed with, the granulated product obtained in step (3), and then the mixture is sprayed with 50 to 150 ml of an aqueous solution containing 2 to 20 g glucose for 5 to 30 minutes at a rate of 5 to 10 ml/min. and then dried at 60 to 80 °C whereby the glucose powder is allowed to adhere to the surface of the product to form a fourth layer thereon. Although the thickness of the fourth layer is not uniform, the solid organic acid is coated with the aqueous solution containing glucose. To improve adhesion of the glucose powder to the product said aqueous solution may contain sodium chloride. The water content in the granulated product after drying is preferably 0.1 to 2 %.

(5) 350 to 600 g sodium bicarbonate powder with a particle diameter of 0.03 to 0.5 mm is introduced into, and mixed with, the granulated product obtained in step (4), and the mixture is sprayed with 50 to 250 ml aqueous solution containing 4 to 40 g glucose for 5 to 50 minutes at a rate of 5 to 10 ml/min. and then dried at 50 to 70 °C thereby allowing the sodium bicarbonate powder to adhere to the surface of the product to form a fifth layer. Although the thickness of the fifth layer is not uniform, the sodium bicarbonate is coated with the aqueous solution containing glucose. The water content in the product after drying is preferably 0.1 to 2 %. After the fifth layer is formed, the particles are dried at 50 to 70 °C for 3 to 30 minutes whereby a solid pharmaceutical preparation for dialysis is obtained as the final granulated product. The solid pharmaceutical preparation for dialysis has a particle diameter of 0.2 to 2 mm with a water content of 0.1 to 0.5 %.

Examples

[0032] Hereinafter, the present invention is described in more detail by reference to the following examples, which however are not intended to limit the present invention.

Example 1

[0033] 1,282 g sodium chloride with an average particle diameter of 0.4 mm was introduced as nucleating particles into a granulation drying unit for rotatively fluidizing (Multiplex MP-01 model, manufactured by Powrex) and sprayed for 20 minutes with a total of 350 ml of an aqueous solution containing 104 g sodium acetate at a spraying temperature of 80 °C and simultaneously dried to form a first layer thereon. An equant (or cubic) particle of sodium chloride is shown in Fig. 2, and a particle having the first layer formed on the surface of the sodium chloride particle is shown in Fig. 3. Then, the particles were sprayed for 15 minutes with a total of 150 ml of an aqueous solution containing 42 g calcium chloride, 23 g magnesium chloride and 34 g potassium chloride at a spraying temperature of 80 °C and simultaneously dried to form a second layer thereon. A particle having the second layer formed thereon is shown in Fig. 4. Further, these particles were sprayed for 15 minutes with a total of 70 ml of an aqueous solution containing 34 g citric acid at a spraying temperature of 80 °C and simultaneously dried to form a third layer thereon. A particle having the third layer formed thereon is shown in Fig. 5. 165 g glucose powder with a particle diameter of 0.07 to 0.4 mm was introduced into, and mixed with, the particles which were then sprayed for 8 minutes with a total of 50 ml of an aqueous solution containing 10 g glucose and 20 g sodium chloride at a spraying temperature of 60 °C and simultaneously dried to form a fourth layer thereon. A particle having the fourth layer formed thereon is shown in Fig. 6. Then, 544 g sodium bicarbonate powder with a particle diameter of 0.05 to 0.2 mm was introduced into, and mixed with, the particles which were then sprayed for 15 minutes with a total of 100 ml of aqueous solution containing 20 g glucose and 20 g sodium chloride at a spraying temperature of 60 °C and simultaneously dried to form a fifth layer thereon. Thereafter, the particles were further dried at 60 °C for 15 minutes to give a solid pharmaceutical preparation for dialysis with an average particle diameter of 0.8 mm as a final granulated product. The solid pharmaceutical preparation for dialysis as the final granulated product is shown in Fig. 7, and a section of the pharmaceutical preparation for dialysis is shown in Fig. 8.

[0034] From 2,200 g of the resulting solid pharmaceutical preparation for dialysis, 52.5 g was taken thrice arbitrarily

and each batch of the preparation was dissolved in water to prepare 5 L of a dialysis solution. The contents of the respective ingredients in each dialysis solution were measured. The results are shown in Table 1. Na^+ and K^+ were determined by flame spectrometry, Ca^{2+} and Mg^{2+} by atomic absorption photometry, Cl^- by titration with silver nitrate, CH_3COO^- , citric acid and glucose by liquid chromatography, and HCO_3^- by ion chromatography.

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Table 1

	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	CH_3COO^-	HCO_3^-	Citric acid	Glucose
First time	141.2	1.97	2.53	1.01	113.6	5.52	27.5	2.43	90
Second time	139.1	1.92	2.42	0.99	110.2	5.29	29.6	2.52	97
Third time	140.3	1.95	2.46	1.02	112.4	5.38	28.0	2.35	94
Mean	140.2	1.95	2.47	1.01	112.1	5.40	28.4	2.43	94
Standard deviation	0.9	0.02	0.05	0.01	1.4	0.09	0.9	0.07	3

Unit: Glucose, mg/dL; others, mEq/L

[0035] As is evident from Table 1, the solid pharmaceutical preparation for dialysis according to the present invention was excellent in the uniformity of the respective ingredients with a standard deviation of 1.4 or less.

[0036] Further, from 2,200 g of the resulting solid pharmaceutical preparation for dialysis, 52.5 g was taken arbitrarily and introduced into an aluminum laminated bag having gas barrier properties (thickness, 104 μm ; outer layer, polyethylene terephthalate (12 μm); intermediate layer, aluminum (12 μm); inner layer, linear low-density polyethylene (80 μm)) and stored at 40 °C for 3 months. Comparison after this storage indicated that, as compared with the solid pharmaceutical preparation for dialysis before storage, there was neither change in the contents of the ingredients nor coloration thereof.

[0037] Further, the solid pharmaceutical preparation for dialysis after storage for 3 months was dissolved in reverse-osmotic water to prepare 5 L of a dialysis solution, and separately 52.5 g of the solid pharmaceutical preparation for dialysis before storage was dissolved in reverse-osmotic water to prepare a dialysis solution. Comparison therebetween indicated that there was neither coloration in the solution nor change in the pH value.

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Effect of the Invention

[0038] The solid pharmaceutical preparation for dialysis according to the present invention is a coated granule, particle or powder consisting of nucleating particles made of sodium chloride and 5 layers consisting of first to fifth layers on said nucleating particles, thereby making it possible to prevent generation of carbon dioxide by reaction of sodium bicarbonate with a solid organic acid, formation of carbonates by reaction of sodium bicarbonate with electrolytes and formation of acetic acid by reaction of a solid organic acid with sodium acetate.

[0039] Further, glucose and sodium bicarbonate are used as coatings in the form of non-pulverized crystals whereby the step of pulverizing glucose and sodium bicarbonate can be omitted thereby simplifying the step of granulating the solid pharmaceutical preparation for dialysis.

[0040] Further, in the process for producing the solid pharmaceutical preparation for dialysis according to the present invention, the ingredients added in a large amount, such as sodium chloride, glucose and sodium bicarbonate are used in the form of powder while the ingredients in a small amount, such as potassium chloride, calcium chloride, magnesium chloride, sodium acetate and a solid organic acid are dissolved in water to be used as aqueous solutions for coating, thereby achieving not only uniformity of the ingredients in the solid pharmaceutical preparation for dialysis but also simplification of the granulation step.

Claims

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1. A solid pharmaceutical preparation for dialysis comprising an electrolyte for hemodialysis, a solid organic acid and glucose and being in the form of a plurality of layers on the surface of a nucleating particle of sodium chloride, wherein the plurality of layers (A), (B) and (C) are not in contact with each other and consist essentially of a layer (A) comprising sodium acetate but not containing the solid organic acid, a layer (B) comprising the solid organic acid but not containing sodium acetate, and a layer (C) comprising sodium bicarbonate.
2. The solid pharmaceutical preparation for dialysis according to claim 1, wherein layer (C) is an outermost layer.

3. The solid pharmaceutical preparation for dialysis according to claim 1, wherein the electrolyte for hemodialysis comprises sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium acetate and sodium bicarbonate.
- 5 4. The solid pharmaceutical preparation for dialysis according to claim 1, wherein the solid organic acid is one or more acids selected from the group consisting of citric acid, oxalic acid, tartaric acid, maleic acid, ascorbic acid, oxaloacetic acid, isocitric acid and malic acid.
- 10 5. A solid pharmaceutical preparation for dialysis according to claim 1, which comprises a nucleating particle consisting of sodium chloride and, in order, a first layer (A) on said nucleating particle and containing sodium acetate but not containing a solid organic acid, a second layer containing at least one ingredient selected from the group consisting of calcium chloride, magnesium chloride, potassium chloride and sodium chloride but not containing sodium acetate and not containing a solid organic acid, a third layer (B) containing a solid organic acid but not containing sodium acetate, a fourth layer containing glucose powder and a fifth layer (C) containing sodium bicarbonate powder.
- 15 6. The solid pharmaceutical preparation for dialysis according to claim 5, wherein the glucose powder and sodium bicarbonate powder are in the form of non-pulverized crystals.
- 20 7. The pharmaceutical preparation for dialysis according to claim 5, wherein the glucose powder and sodium bicarbonate powder are each in the form of crystalline powder with a particle diameter of 0.03 to 0.5 mm.
8. The pharmaceutical preparation according to claim 1, wherein the solid organic acid is citric acid.
- 25 9. A process for producing a pharmaceutical preparation for dialysis comprising forming a layer (A) containing sodium acetate but not containing solid organic acid on the surface of a nucleating particle consisting of sodium chloride, forming a layer (B) containing a solid organic acid on the surface of the nucleating particle, and forming a layer (C) containing sodium bicarbonate on the surface of the nucleating particle in this order, said layer (B) not contacting said layer (A) and said layer (C) not contacting said layer (B).
- 30 10. A process for producing a pharmaceutical preparation for dialysis according to claim 9, comprising:
- 35 (a) spraying an aqueous solution containing sodium acetate but not containing a solid organic acid on the surface of nucleating particles consisting of sodium chloride, and drying the particles,
- (b) spraying the particles obtained in step (a) with an aqueous solution containing at least one ingredient selected from the group consisting of calcium chloride, magnesium chloride, potassium chloride and sodium chloride but not containing sodium acetate and not contacting a solid organic acid, and drying the particles,
- 40 (c) spraying the particles obtained in step (b) with an aqueous solution containing a solid organic acid and not containing sodium acetate and drying the particles,
- (d) mixing glucose powder with the particles obtained in step (c), then spraying the particles with an aqueous solution containing glucose and/or sodium chloride and drying the particles, and
- (e) mixing sodium bicarbonate powder with the particles obtained in step (d), then spraying the particles with an aqueous solution containing glucose and/or sodium chloride and drying the particles.
- 45 11. The process for producing a solid pharmaceutical preparation for dialysis according to claim 9, wherein the glucose powder and sodium bicarbonate powder are in the form of non-pulverized crystals.
12. The process for producing a solid pharmaceutical preparation for dialysis according to claim 9, wherein the glucose powder and sodium bicarbonate powder are in the form of crystals with a particle diameter of 0.03 to 0.5 mm.
- 50 13. The process for producing a solid pharmaceutical preparation for dialysis according to claim 9, wherein the solid organic acid is citric acid.

55 **Patentansprüche**

1. Feste pharmazeutische Zubereitung zur Dialyse, umfassend einen Elektrolyten für die Hämodialyse, eine feste organische Säure und Glucose, wobei sie in der Form einer Vielzahl von Schichten auf der Oberfläche eines

5 kernbildenden Natriumchlorid-Teilchens vorliegt, wobei die Vielzahl von Schichten (A), (B) und (C) sich nicht in Kontakt miteinander befinden und im Wesentlichen aus einer Schicht (A), welche Natriumacetat umfasst, aber keine feste organische Säure enthält, einer Schicht (B), welche die feste organische Säure umfasst, aber kein Natriumacetat enthält, und einer Schicht (C), welche Natriumbicarbonat umfasst, bestehen.

- 10 2. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 1, worin die Schicht (C) eine äußerste Schicht ist.
- 15 3. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 1, worin der Elektrolyt für die Hämodialyse Natriumchlorid, Calciumchlorid, Magnesiumchlorid, Kaliumchlorid, Natriumacetat und Natriumbicarbonat umfasst.
- 20 4. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 1, worin die feste organische Säure eine oder mehrere Säuren, ausgewählt aus der Gruppe bestehend aus Zitronensäure, Oxalsäure, Weinsäure, Maleinsäure, Ascorbinsäure, Oxalelligsäure, Isozitronensäure und Äpfelsäure, ist.
- 25 5. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 1, die ein kernbildendes Teilchen aus Natriumchlorid und, in dieser Reihenfolge, eine erste Schicht (A) auf dem kernbildenden Teilchen, die Natriumacetat, aber keine feste organische Säure enthält, eine zweite Schicht, die mindestens einen Inhaltsstoff, ausgewählt aus der Gruppe bestehend aus Calciumchlorid, Magnesiumchlorid, Kaliumchlorid und Natriumchlorid, aber kein Natriumacetat und keine feste organische Säure enthält, eine dritte Schicht (B), die eine feste organische Säure, aber kein Natriumacetat enthält, eine vierte Schicht, die Glucosepulver enthält, und eine fünfte Schicht (C), die Natriumbicarbonatpulver enthält, umfasst.
- 30 6. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 5, worin das Glucosepulver und das Natriumbicarbonatpulver in der Form nicht pulverisierter Kristalle vorliegen.
- 35 7. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 5, worin das Glucosepulver und das Natriumbicarbonatpulver jeweils in der Form kristallinen Pulvers mit einem Teilchendurchmesser von 0,03 bis 0,5 mm vorliegen.
- 40 8. Feste pharmazeutische Zubereitung zur Dialyse nach Anspruch 1, worin die feste organische Säure Zitronensäure ist.
- 45 9. Verfahren zur Herstellung einer pharmazeutischen Zubereitung zur Dialyse, umfassend die Bildung einer Schicht (A), die Natriumacetat, aber keine feste organische Säure umfasst, auf der Oberfläche eines kernbildenden Teilchens, das aus Natriumchlorid besteht, die Bildung einer Schicht (B), die eine feste organische Säure enthält, auf der Oberfläche des kernbildenden Teilchens und die Bildung einer Schicht (C), die Natriumbicarbonat enthält, auf der Oberfläche des kernbildenden Teilchen in dieser Reihenfolge, wobei die Schicht (B) die Schicht (A) nicht berührt und die Schicht (C) nicht die Schicht (B) berührt.
- 50 10. Verfahren zur Herstellung einer pharmazeutischen Zubereitung zur Dialyse nach Anspruch 9, umfassend:
- 55 (a) Aufsprühen einer wässrigen Lösung, die Natriumacetat, aber keine feste organische Säure enthält, auf die Oberfläche von kernbildenden Teilchen, die aus Natriumchlorid bestehen, und Trocknen der Teilchen,
- (b) Besprühen der in Stufe (a) erhaltenen Teilchen mit einer wässrigen Lösung, die mindestens einen Inhaltsstoff enthält, welcher aus der Gruppe, bestehend aus Calciumchlorid, Magnesiumchlorid, Kaliumchlorid und Natriumchlorid ausgewählt ist, die aber kein Natriumacetat enthält und nicht mit einer festen organischen Säure in Kontakt steht, und Trocknen der Teilchen,
- (c) Besprühen der in Stufe (b) erhaltenen Teilchen mit einer wässrigen Lösung, die eine feste organische Säure und kein Natriumacetat enthält, und Trocknen der Teilchen,
- (d) Mischen von Glucosepulver mit den in Stufe (c) erhaltenen Teilchen, anschließendes Besprühen der Teilchen mit einer wässrigen Lösung, die Glucose und/oder Natriumchlorid enthält, und Trocknen der Teilchen und
- (e) Mischen von Natriumbicarbonatpulver mit den in Stufe (d) erhaltenen Teilchen, anschließendes Besprühen der Teilchen mit einer wässrigen Lösung, die Glucose und/oder Natriumchlorid enthält, und Trocknen der Teilchen.
- 55 11. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung zur Dialyse nach Anspruch 9, worin das Glucosepulver und das Natriumbicarbonatpulver in der Form nicht pulverisierter Kristalle vorliegen.

12. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung zur Dialyse nach Anspruch 9, worin das Glucosepulver und das Natriumbicarbonatpulver in der Form von Kristallen mit einem Teilchendurchmesser von 0,03 bis 0,5 mm vorliegen.
- 5 13. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung zur Dialyse nach Anspruch 9, worin die feste organische Säure Zitronensäure ist.

Revendications

- 10 1. Préparation pharmaceutique solide pour la dialyse, comprenant un électrolyte pour hémodialyse, un acide organique solide et du glucose, et qui se présente sous forme de couches multiples à la surface d'une particule de nucléation constituée de chlorure de sodium, dans laquelle les couches multiples (A), (B) et (C) ne sont pas en contact les unes avec les autres et sont constituées essentiellement d'une couche (A) comprenant de l'acétate de sodium mais ne contenant pas l'acide organique solide, d'une couche (B) comprenant l'acide organique solide mais ne contenant pas d'acétate de sodium, et d'une couche (C) comprenant du bicarbonate de sodium.
- 15 2. Préparation pharmaceutique solide pour la dialyse selon la revendication 1, dans laquelle la couche (C) est la couche la plus à l'extérieur.
- 20 3. Préparation pharmaceutique solide pour la dialyse selon la revendication 1, dans laquelle l'électrolyte pour hémodialyse comprend du chlorure de sodium, du chlorure de calcium, du chlorure de magnésium, du chlorure de potassium, de l'acétate de sodium et du bicarbonate de sodium.
- 25 4. Préparation pharmaceutique solide pour la dialyse selon la revendication 1, dans laquelle l'acide organique solide est un ou plusieurs acides choisis dans le groupe constitué par l'acide citrique, l'acide oxalique, l'acide tartrique, l'acide maléique, l'acide ascorbique, l'acide oxaloacétique, l'acide isocitrique et l'acide malique.
- 30 5. Préparation pharmaceutique solide pour la dialyse selon la revendication 1, qui comprend une particule de nucléation constituée de chlorure de sodium et, dans l'ordre, une première couche (A) qui se trouve sur ladite particule de nucléation et contenant de l'acétate de sodium mais ne contenant pas d'acide organique solide, une deuxième couche contenant au moins un ingrédient choisi dans le groupe constitué par le chlorure de calcium, le chlorure de magnésium, le chlorure de potassium et le chlorure de sodium mais ne contenant pas d'acétate de sodium ni d'acide organique solide, une troisième couche (B) contenant un acide organique solide mais ne contenant pas d'acétate de sodium, une quatrième couche contenant de la poudre de glucose et une cinquième couche (C) contenant de la poudre de bicarbonate de sodium.
- 35 6. Préparation pharmaceutique solide pour la dialyse selon la revendication 5, dans laquelle la poudre de glucose et la poudre de bicarbonate de sodium sont sous forme de cristaux non pulvérisés.
- 40 7. Préparation pharmaceutique pour la dialyse selon la revendication 5, dans laquelle la poudre de glucose et la poudre de bicarbonate de sodium sont chacune sous forme d'une poudre cristalline ayant un diamètre de particule de 0,03 à 0,5 mm.
- 45 8. Préparation pharmaceutique selon la revendication 1, dans laquelle l'acide organique solide est l'acide citrique.
9. Procédé pour produire une préparation pharmaceutique pour la dialyse, comprenant la formation d'une couche (A) contenant de l'acétate de sodium mais ne contenant pas d'acide organique solide à la surface d'une particule de nucléation constituée de chlorure de sodium, la formation d'une couche (B) contenant un acide organique solide à la surface de la particule de nucléation, et la formation d'une couche (C) contenant du bicarbonate de sodium à la surface de la particule de nucléation, dans cet ordre, ladite couche (B) n'étant pas au contact de ladite couche (A) et ladite couche (C) n'étant pas au contact de ladite couche (B).
- 50 10. Procédé pour produire une préparation pharmaceutique pour la dialyse selon la revendication 9, comprenant:
- 55 (a) la pulvérisation d'une solution aqueuse contenant de l'acétate de sodium mais ne contenant pas d'acide organique solide à la surface de particules de nucléation constituées de chlorure de sodium, et le séchage des particules,

(b) la pulvérisation des particules obtenues dans l'étape (a) avec une solution aqueuse contenant au moins un ingrédient choisi dans le groupe constitué par le chlorure de calcium, le chlorure de magnésium, le chlorure de potassium et le chlorure de sodium, mais ne contenant pas d'acétate de sodium et n'étant pas au contact d'un acide organique solide, et le séchage des particules,

5 (c) la pulvérisation des particules obtenues dans l'étape (b) avec une solution aqueuse contenant un acide organique solide et ne contenant pas d'acétate de sodium et le séchage des particules,

(d) le mélange d'une poudre de glucose avec les particules obtenues dans l'étape (c), puis la pulvérisation des particules avec une solution aqueuse contenant du glucose et/ou du chlorure de sodium et le séchage des particules, et

10 (e) le mélange d'une poudre de bicarbonate de sodium avec les particules obtenues dans l'étape (d), puis la pulvérisation des particules avec une solution aqueuse contenant du glucose et/ou du chlorure de sodium et le séchage des particules.

15 11. Procédé pour produire une préparation pharmaceutique solide pour la dialyse selon la revendication 9, dans lequel la poudre de glucose et la poudre de bicarbonate de sodium sont sous forme de cristaux non pulvérisés.

12. Procédé pour produire une préparation pharmaceutique solide pour la dialyse selon la revendication 9, dans lequel la poudre de glucose et la poudre de bicarbonate de sodium sont sous forme de cristaux ayant un diamètre de particule de 0,03 à 0,5 mm.

20 13. Procédé pour produire une préparation pharmaceutique solide pour la dialyse selon la revendication 9, dans lequel l'acide organique solide est l'acide citrique.

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Fig. 1

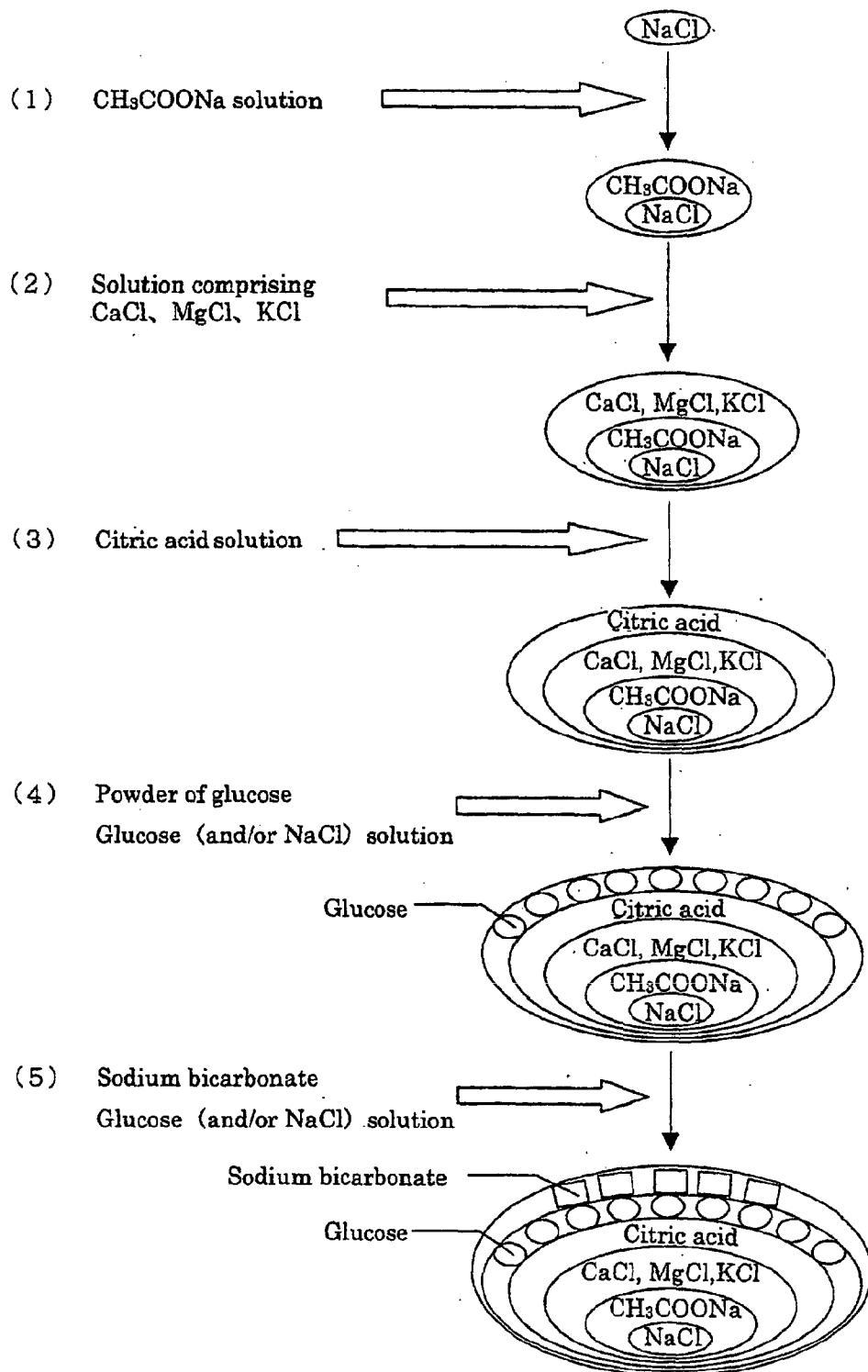


Fig. 2

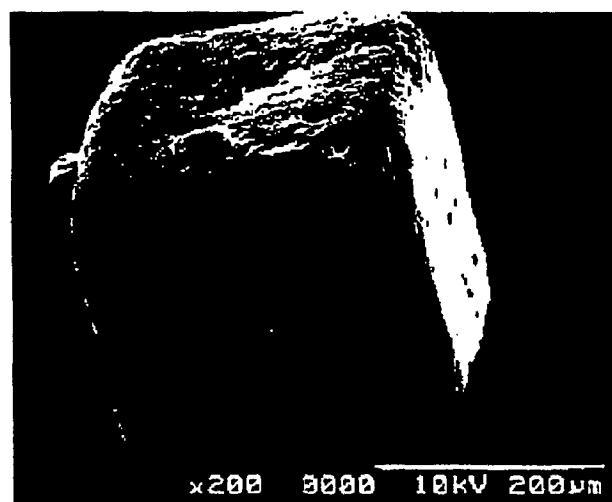


Fig. 3

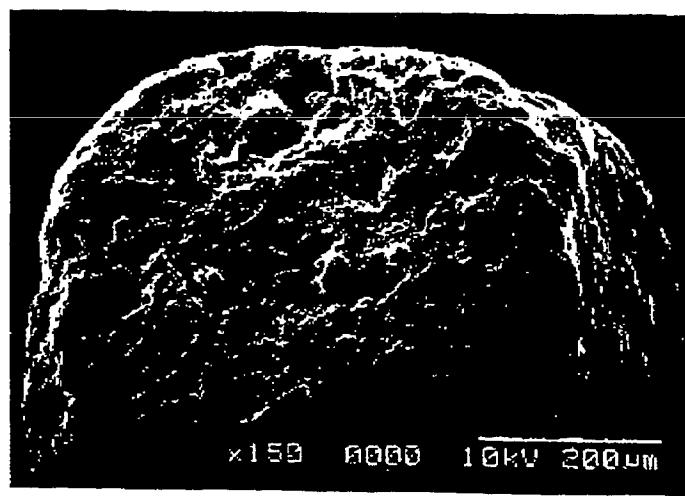


Fig. 4

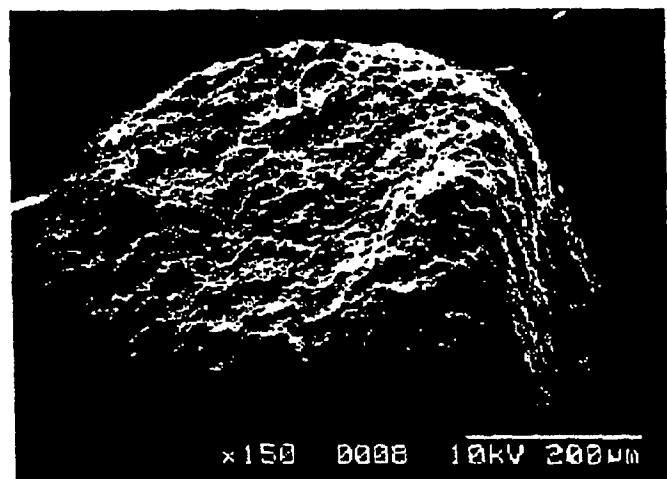


Fig. 5

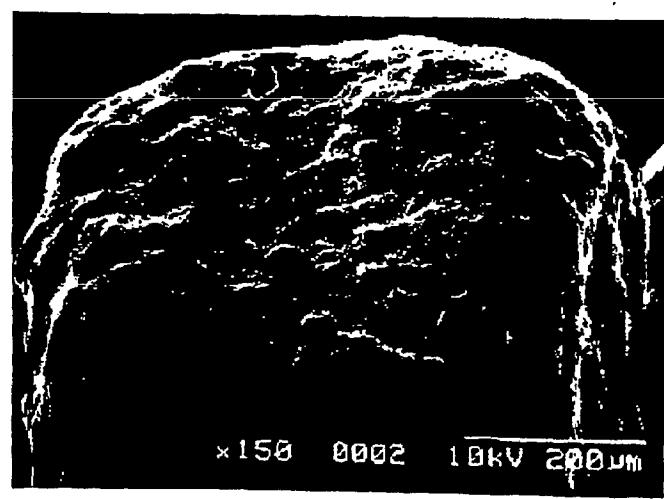


Fig. 6



Fig. 7

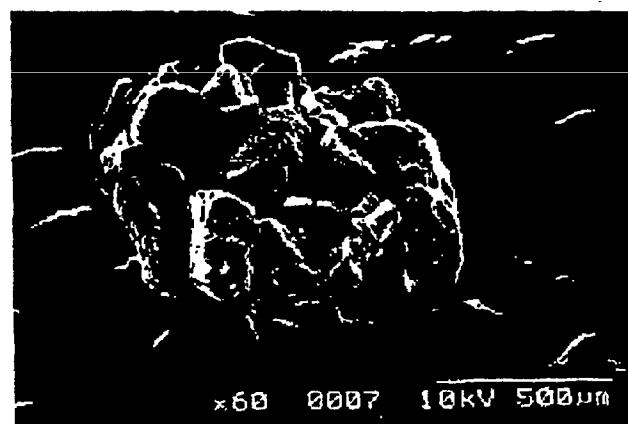


Fig. 8

